Neuroblastoma

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45.1 Introduction

This condition was first described in 1864 by the German physician Rudolf Virchow who called the tumors he found in the abdomens of children *gliomas*. In 1910, James Homer Wright noted that these tumors originated from an immature, primitive form of neural cell and he, therefore, named the tumors *neuroblasts*. He also documented the formation of round clumps of cells in samples of bone marrow and this feature has become the histological characteristic of the disease and is commonly referred to as *"Homer–Wright pseudorosettes."* Figure 45.1

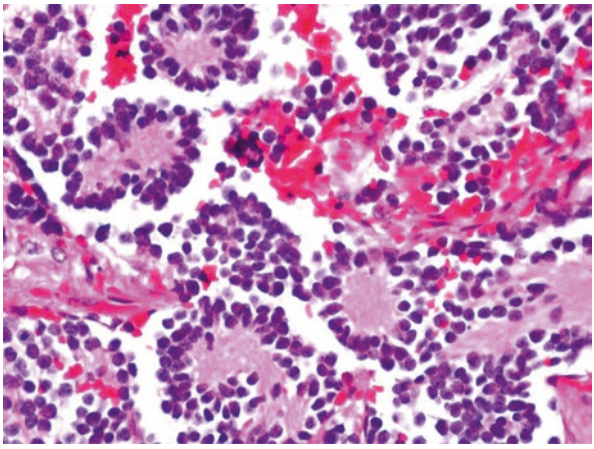

Fig. 45.1 Pseudorosette formation in adrenal neuroblastoma [picture courtesy of Ed Uthman, reproduced under Creative Commons]

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- This is the third most common cancer of childhood after leukemia and brain cancer (5–10%) with almost 100 affected children/year in the UK.
- Age of onset Infancy ~30%.
- 1–4 years ~50%
- 10–14 years ~5%
- M > F (slight).
- White> Black > Asian.

45.2 Sites of Origin

- Adrenal medulla (~50%).
- Abdominal sympathetic ganglia (~25%).
- Posterior mediastinum (~20%).
- Pelvis (~3%).
- Neck (~3%).

45.3 Pathology

These are soft tumors with areas of hemorrhage and necrosis. More mature areas tend to be firm.

The histological appearance is of sheets of dark blue round cells with scanty cytoplasm, embedded in a delicate vascular stroma and tends to spread with local extension and encasement of major vessels. May metastasize to lymph nodes, bones, bone marrow, liver, and skin. Secondary spread is usually associated with large primaries (except stage MS tumors). There is a characteristic ring of neuroblasts around a neurofibrillary core (*rosette formation*) which differentiate from other blue, round cell tumors (e.g., Ewing's sarcoma, lymphoma, and rhabdomyosarcoma).

45.3.1 Shimada[1] System Classification

Based on the

- Mitosis karyorrhexis index (MKI).
- Age of child.
- Degree of differentiation (toward ganglioneuroma).
- Stroma-rich or stroma-poor.

Favorable prognosis includes infants, low MKI, stroma-rich tumors, well-differentiated tumors, or tumors with intermixed degrees of differentiation.

[1] Hiroyuki Shimada – Japanese pathologist, latterly working in Los Angeles, USA.

45.3.2 Cytogenetics and Prognostic Factors

A large number of molecular abnormalities have been identified in the neuroblastoma cells. These include:

- *MYCN* amplification.
- Gene on Ch 2p leads to activation of angiogenesis pathways and ↑tumor growth.
- Advanced vs. low-stage disease stage (amplification present ~40% vs. ~10%).
- 90% of patients with MYCN amplification will die of disease progression irrespective of treatment modality used
- Ch 17q gain, Ch 1p deletion.
- Expression of the H-*ras* oncogene—associated with low-stage disease.
- DNA ploidy and index—diploid DNA associated with *MYCN* amplification.
- CD44 expression—↑expression associated with good prognosis.
- TRKA expression—↑expression associated with good prognosis.
- Multidrug resistance-associated protein (MRP)—↑ levels associated with poor prognosis.

45.4 Clinical Features

Usually, there is a palpable abdominal mass and unlike other tumors (e.g., Wilms') children often appear sick, lethargic with fatigue, bone pain, weight loss, fever, sweating, and anemia.

Unusual but Characteristic Features

- Periorbital ecchymosis or proptosis (racoon eyes)—retro-orbital secondaries.
- Horner's[2] syndrome—apical thoracic tumors.
- Progressive cerebellar ataxia and trunk opsomyoclonus.
- Dancing eye syndrome—rapid but chaotic, conjugate eye movements.
- Progressive paraplegia—from extradural cord compression.
- Hypertension (~25%) due to catecholamine production or renal artery compression.
- Skin nodules—stage MS disease.
- Diarrhea—due to vasoactive intestinal polypeptide (VIP) release—more typical of ganglioneuromas and ganglioneuroblastomas.

45.4.1 Specific Investigations

- ↑↑*Vanillylmandelic acid (VMA) and homovanillic acid (HVA)*—urinary metabolites of catecholamines
- ↑ferritin, ↑ lactate dehydrogenase (LDH), and ↑ Neuron-specific enolase (NSE)
- AXR—tumor calcification (~50%).
- *US*—solid vs. cystic, may suggest renal vein and caval involvement.

[2] Johann F. Horner (1831–1886) – Swiss ophthalmologist named triad as meiosis, ptosis and enophthalmos, but can have ↓ facial sweating and iris color change. Described many times before Horner's case in 1869.

- *CT/MRI scans*—anatomy of tumor with IDRF identification and search for metastases. Possible intraspinal extension ("dumb-bell" tumor).
- *MIBG (meta-iodobenzylguanidine) scan*—for abnormal medullary tissue and for primary tumor avidity, is useful for post-treatment assessment.
- Technetium-99 bone scintigraphy in selected cases.
- *Biopsy*—percutaneous or laparoscopic/open.
- Bone marrow aspirate and biopsy (bilateral). *Not required under 6 months.*

45.5 Staging: Complex and Evolving

45.5.1 International Neuroblastoma Risk Group (INRG) Classification System

The INRG Taskforce introduced a new staging system *(INRGSS)* (Table 45.1) as a pre-treatment staging system based on *Image Defined Risk Factors (IDRF)* (Table 45.2) as opposed to *International Neuroblastoma Staging System (INSS)* which is the post-surgical treatment staging system.

Table 45.1 INRG task force divided all tumors into 16 pre-treatment groups based on the INRG stage, age, histologic category, grade of tumor differentiation, *MYCN* status, presence/absence of 11q aberrations, and tumor cell ploidy

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS	< 18			NA	No		C Very low
					Yes		Q High
				Amp			R High

INRG consensus pre-treatment classification schema.

Notes: Pre-treatment risk group H has two entries. 12 months = 365 days; 18 months = 547 days; blank field = "any"; diploid (DNA index ≤1.0); hyperdiploid (DNA index >1.0 and includes near-triploid and near-tetraploid tumors); very low risk (5-year EFS > 85%); low risk (5-year EFS > 75% to ≤85%); intermediate risk (5-year EFS ≥ 50% to ≤75%); high risk (5-year EFS < 50%). *GN* ganglioneuroma; *GNB* ganglioneuroblastoma; *amp* amplified; *NA* not amplified; *L1* localized tumor confined to one body compartment and with absence of image-defined risk factors (IDRFs); *L2* locoregional tumor with presence of one or more IDRFs; *M* distant metastatic disease (except stage MS); *MS* metastatic disease confined to skin, liver and/or bone marrow in children <18 months of age; *EFS* event-free survival.

Reference: Cohn SL et al. The International Neuroblastoma Risk Group (INRG) Classification System: An INRG Task Force Report. J Clin Oncol. 2009; 27: 289–297

Table 45.2 Image Defined Risk Factors in Neuroblastic Tumors

Ipsilateral tumor extension within two body compartments
Neck-chest, chest-abdomen, abdomen-pelvis

Neck
- Tumor encasing carotid and/or vertebral artery and/or internal jugular vein.
- Tumor extending to base of skull.
- Tumor compressing the trachea.

Cervico-thoracic junction
Tumor encasing brachial plexus roots
Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
Tumor compressing the trachea

Thorax
- Tumor encasing the aorta and/or major branches.
- Tumor compressing the trachea and/or principal bronchi.
- Lower mediastinal tumor, infiltrating the costo-vertebral junction between T9 and T12.

Thoraco-abdominal
- Tumor encasing the aorta and/or vena cava.

Abdomen/pelvis
- Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament.
- Tumor encasing branches of the superior mesenteric artery at the mesenteric root
- Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
- Tumor invading one or both renal pedicles
- Tumor encasing the aorta and/or vena cava
- Tumor encasing the iliac vessels
- Pelvic tumor crossing the sciatic notch.

Intraspinal tumor extension whatever the location provided that:
- More than one-third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal.
- Infiltration of adjacent organs/structures. Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery.

Conditions to be recorded, but *not* considered IDRFs
Multifocal primary tumors
Pleural effusion, with or without malignant cells
Ascites, with or without malignant cells

45.5.2 INRGSS: International Neuroblastoma Risk Group Staging System

- *Stage L1*: Localized tumor not involving vital structures as defined by the list of *Image Defined Risk Factors* and confined to one body compartment.
- *Stage L2:* Locoregional tumor with presence of one or more *Image Defined Risk Factors.*
- *Stage M:* Distant metastatic disease (except Stage MS).
- *Stage MS:* Metastatic disease confined to *skin, liver, and/or bone marrow in children younger than 18 months of age.*

Table 45.3 International neuroblastoma staging system (INSS) 1989

Stage 1	Localized tumor with complete gross excision, ±microscopic residual disease; representative I/L nodes –ve for tumor microscopically (nodes attached to and removed with the primary tumor may be +ve)
Stage 2A	Localized tumor with incomplete gross excision; representative I/L no adherent lymph nodes negative for tumor microscopically
Stage 2B	Localized tumor ± complete gross excision, with I/L nonadherent lymph nodes +ve for tumor. Enlarged contralateral lymph nodes must be negative microscopically
Stage 3	Unresectable unilateral tumor infiltrating across the midline, ±regional node involvement; or localized unilateral tumor with C/L regional node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by node involvement
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S)
Stage 4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants <1 year). Marrow involvement should be minimal (i.e., <10% of total nucleated cells identified as malignant by bone biopsy or by bone marrow aspirate). More extensive bone marrow involvement would be considered to be stage IV disease. The results of the MIBG scan (if performed) should be –ve for disease in the bone marrow

45.5.3 International Neuroblastoma Staging System (INSS)

The Children Oncology Group (USA) introduced the International Neuroblastoma staging system in 1989. This is relevant for the post-surgical staging of tumors (Table 45.3).

45.6 Management

- *Immediate resection*
  - current practice suggests that this is reserved for tumors in the absence of *image defined risk factors* (IDRF) i.e. (INRG "L1 TUMORS").
- *Tumor biopsy*
  - treatment of metastatic and localized tumors with IDRF's (INRG "L2 Tumors") can be influenced by their *MYCN* status.

Descriptions of very-low, low-risk, intermediate-risk, or high-risk neuroblastoma according to INRG definitions and pre-treatment groups (Table 45.2) are listed below.

45.6.1 Very Low-Risk Neuroblastoma

- Stage L1/L2 with ganglioneuroma maturing or ganglioneuroblastoma intermixed histology
- Stage L1 with non-amplified *MYCN*
- Stage MS in children younger than 18 months of age with no 11q aberration

45.6.2 Low-Risk Neuroblastoma

- Stage L2 in children younger than 18 months of age with no11q aberration
- Stage L2 in children older than 18 months of age with ganglioneuroblastoma nodular or neuroblastoma with differentiating histology and no 11q aberration
- Stage M in children younger than 18 months without *MYCN* amplification and hyperdiploidy

Treatment is tailored according to the risk assignment. Most patients with very-low and low-risk disease commonly receive surgery alone. Sometimes, infants with small-localized tumors have been successfully watched closely without any surgery, tumor may mature and regress.

45.6.2.1 Proposed Criteria for Observation

- Age at presentation
- Suprarenal mass measuring <5 cm on US
- No IDRF
- No evidence of metastases on MIBG
- Stable or decreasing size on regular US
- Stable or decreasing catecholamines on regular urinalysis

45.6.3 Intermediate-Risk Neuroblastoma

- Stage L2 in children younger than 18 months without *MYCN* amplification with 11q aberration
- Stage L2 in children older than 18 months with ganglioneuroblastoma nodular or neuroblastoma with differentiating histology with 11q aberration
- Stage L2 in children older than 18 months with ganglioneuroblastoma nodular or neuroblastoma with poorly differentiated or undifferentiated histology
- Stage M in children younger than 12 months with diploidy
- Stage M in children 12 months to 18 months with diploidy

Patients with intermediate-risk disease receive surgery and chemotherapy. Number of cycles of chemotherapy is determined by associated risk factors including tumor histology, genetic changes associated with chromosome 1p and 11q, ploidy, and age at presentation.

45.6.4 High-Risk Neuroblastoma

- Stage L1 with *MYCN* amplification
- Stage L2 with *MYCN* amplification
- Stage M in children <18 months of age with *MYCN* amplification
- Stage M in children >18 months

- Stage MS in children <18 months with 11q aberration
- Stage MS in children <18 months of age with *MYCN* amplification

Multi-agent intensive induction chemotherapy to induce tumor remission, and improve chance of resection. Surgery to excise the tumor is then carried out.

Further high-dose chemotherapy and peripheral stem cell rescue for reconstitution of patient's bone marrow ± retinoic acid ± radiotherapy.

Outcome of Neuroblastoma
* 85–90% survival—low /intermediate risk tumors
* <50% - high risk tumors

45.7 Fetal Tumors

Increasingly frequent clinical scenario. Most have favorable biologic markers with no *MYCN* amplification (i.e., Very Low Risk with excellent survival following surgery alone). Some advocate observation only in the early management expecting regression and small (<5 cm) tumors appear to be good candidates for this approach. About 60% of infants can avoid surgery following spontaneous tumor regression.

45.8 Spinal Cord Compression

Spinal cord compression by dumb-bell type tumors may cause paralysis, paresthesia, or bladder dysfunction. Immediate treatment is mandatory. Treatment options include surgical decompression of the spinal cord, steroids with chemotherapy or radiotherapy. In asymptomatic patients, extraspinal tumor resection is sufficient.

45.9 Surgery

- Aim of surgery in very low-risk and low-risk tumors is to do a complete resection. No chemotherapy is required once tumor is completely removed.
- Aim of surgery post chemotherapy in intermediate and high-risk tumors is to achieve complete resection. However, this may not always be possible as tumor may be adherent to vital structures.
- Near-complete excision (microscopic residual only) is also associated with a better prognosis in high-risk tumors.
- Aim of second-look procedure is to achieve as complete a debulking as possible without sacrificing major organ function.

Possible role for laparoscopic and thoracoscopic surgery is diagnostic and excision biopsies of smaller tumors. This is evolving in nature as the laparoscopic gadgets are refined and skill level is increasing.

45.10 New Treatments

- I^{131} labeled MIBG.
- New chemotherapy agents—topotecan, irinotecan, etoposide, oral topoisomerase II inhibitor.
- Immunologic therapies include monoclonal antibodies, cytokine therapies, and vaccines.
- Antiangiogenic factors.
- Other experimental agents include tyrosine kinase inhibitors, direct targeting of *MYCN* amplified cells, and creation of chimeric antibodies to deliver cytotoxic drugs.

Further Reading

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